PART 2: NON-TECHNICAL ABSTRACT

The purpose of this Phase 2 clinical research study sponsored by Genzyme Corporation is to examine the safety of an experimental gene transfer agent, Ad2/HIF-1α/VP16, and its ability to stimulate the growth of new blood vessels from existing blood vessels (a process called angiogenesis) in an attempt to improve the flow of blood in the legs of patients with peripheral arterial disease (PAD). Specifically, this study will enroll patients with severe intermittent claudication (IC) which is the stage of PAD in which a patient's walking ability is severely limited, causing pain in the legs upon exercise due to inadequate blood flow to the muscles of the lower limbs. HIF-1α is naturally produced by the body in response to low tissue oxygen levels and is responsible for turning on several growth factors involved in the angiogenesis process. These growth factors, called angiogenic growth factors, have the ability to stimulate the growth of new blood vessels from existing blood vessels and, as a result, potentially increase the flow of blood carrying oxygen to these cells.

Although the gene being transferred into the patients in this study, HIF-1α/VP16, is closely related to natural HIF-1α, it is not identical to the natural substance produced by the body. Genzyme has genetically altered it so it has certain important biological characteristics that may promote more robust angiogenesis. Any new blood vessels that may form may increase the flow of blood to the muscles in the leg. Increased blood flow to the leg muscles may reduce the pain (claudication) in the legs upon walking.

The altered gene for HIF-1 α will be introduced into the cells by using a modified virus called an adenovirus. Adenovirus Type 2 (Ad2) is a common virus found in human airways. In general, adenovirus infections result in mild cold-like symptoms. More serious infections by an adenovirus can result in bronchitis, croup, and pneumonia. The adenovirus used in this study has been altered in the laboratory so that it is unable to replicate and thereby unable to cause the above mentioned illnesses.

Genzyme conducted extensive pre-clinical studies in animal models to test for safety and preliminary efficacy before initiating the Phase 1 studies (NIH protocols 9907-327/-328/-329) in patients with critical limb ischemia (CLI), a severe form of PAD characterized by pain while at rest, and/or, with skin ulceration. Overall, the results from the PAD Phase 1 program in the CLI patients showed Ad2/HIF-1α/VP16 to be well tolerated. Other than mild to moderate injection site reactions, no adverse drug reactions have been

identified in these studies. No safety problems emerged that would prevent Ad2/HIF-1α/VP16 from being tested in patients with PAD. Although the Phase 1 study (total of 38 patients, 34 of whom received Ad2/HIF-1 α/VP16) was not intended to determine if the gene transfer works, some patients demonstrated clinical improvements of rest pain resolution and complete ulcer healing. However, others had worsening of their symptoms and required amputation.

The proposed Phase 2 clinical study will be conducted in a different patient population than the Phase 1 studies. This Phase 2 study will enroll PAD patients with severe IC who can only walk between 1 and 10 minutes before having to stop due to claudication pain, but whose disease has not progressed as far as CLI. The primary goals of the study will be to evaluate safety measures throughout the study and to evaluate if patients have improvement in their walking ability 6 months after receiving the study drug by using a standardized walking treadmill test. Patient Questionnaires pertaining to general health and walking also will be completed. In addition, imaging tests such as magnetic resonance angiography (MRA) and specific blood flow measurements will be done at selected investigational sites where equipment is available to evaluate changes in the appearance of blood vessels and blood flow in the legs.

The Phase 2 study will look at whether different doses of Ad2/HIF-1α/VP16 can be tolerated safely by direct injection into the leg muscles where the blood flow is not sufficient to meet the oxygen demands of the leg muscles. The study design is a randomized, double-blind, placebo-controlled, parallel group, multicenter, Phase 2 dose-selection study. Seventy-five patients will be enrolled into each of 4 study drug groups (3 groups of Ad2/HIF-1α/VP16 gene transfer and 1 placebo group) for a total of 300 patients overall. Three different doses of Ad2/HIF-1α/VP16 gene transfer will be studied. The dose range was previously tested in animals and in the Phase 1 human studies. A placebo group is included in the study to compare safety and efficacy of different doses of Ad2/HIF-1α/VP16 with placebo. Each patient will receive a single set of 20 injections (100 μL each) of gene transfer or placebo in one administration to each leg for a total of 40 injections.

The duration of each patient's participation in the study will be 2 years. It is important to the future development of Ad2/HIF-1α/VP16 that longer term safety data are obtained and that potential favorable effects are maintained for a sufficient period of time to

benefit the patient. Patients will have scheduled follow-up visits at Day 1 and Weeks 1, 4, 12, 26 (6 mo.), and 52 (12 mo.). Within the protocol, specific safety assessments have been included to monitor for potential adverse experiences that could be related to either the adenovirus in which the gene is placed, the HIF-1α/VP16 gene contained in the adenovirus, the direct injection of the study drug or placebo into the leg muscle, or the progression of the patient's underlying disease. At these visits, changes from baseline in physical exams, vital signs, clinical lab tests, and eye examinations will be assessed. All adverse events will be monitored. Additional extended follow-up visits at 78 weeks (18 mo.) and 104 weeks (2 yr) will focus on assessment of PAD disease progression as well as potential significant longer term risks associated with the study drug. After that, patients will be asked to consider participation in a Long Term Follow-up program (up to 15 years) to be conducted under a separate protocol according to national regulations for the conduct of gene transfer trials.

Patients will be screened for cancer at baseline and again at year 1 and year 2 to assess for any unintended blood vessel growth (for example, in support of a tumor). Further, patient samples (i.e., blood, urine, throat swab, and semen-if feasible) also will be collected to assess the potential for presence of the adenovirus in these samples.

A Data Monitoring Committee (DMC) comprised of independent physicians (not conducting the study) will provide an ongoing, expert review of safety data to assure that the risks to study patients are minimized. This ongoing review will include pre-specified interim analyses of safety data during the conduct of the study. The DMC will conduct the first interim assessment of patient safety when the first 60 patients have received study drug (gene transfer or placebo) and been followed for at least 4 weeks. The DMC will be unblinded (that is, they will know which patients received the gene transfer and which received placebo) in their review of this initial 60 patients' safety data. Enrollment at that time will be paused until the DMC authorizes it to continue.

Thereafter, DMC reviews of patient safety will occur in a blinded manner (unless unblinding is specifically requested by the DMC) after each additional cohort of 60 patients (i.e., 120, 180, and 240 patients), enrolled and received study drug, have completed 4 weeks of follow-up. Suspending enrollment for these reviews will only be required if specified by the DMC. The DMC can suspend enrollment or request to see unblinded data at any time.